REMARKS

Claim 1 was amended solely to advance prosecution to gain allowance. The amendments and the corresponding cancellation of claims are advanced without prejudice or disclaimer, are not an admission on the propriety of any rejection and argument provided by the Examiner, and all subject matter disclosed but not claimed in the instant application is subject to continuing prosecution.

I. Beginning on page 3 of the Office Action, claims 1-8, 16 and 18-22 were rejected under 35 U.S.C. 112, first paragraph for an alleged want of enablement. Essentially, the Examiner took the position that not any sugar can be used. For example, the Examiner believed that an aldonic acid cannot be made if a sugar does not have a reducing end.

The rejection is traversed for the following reasons.

As argued in the record, an artisan familiar with carbohydrate chemistry would understand the full scope of the disclosure and the practice thereof. Nevertheless, to advance prosecution and not to be construed as an acquiescence to the position of the Examiner, Applicant focused the claims herein on embodiments of interest. Use of hydroxyethyl starch and N-hydroxy-succinimide as exemplifications of the subject matter of interest is provided throughout the specification, such as, in the working examples.

Clearly, the instant specification teaches how to make and how to use the subject matter of interest. Hence, a prima facie case of non-enablement does not exist and the rejection must be withdrawn.

II. Beginning on page 7 of the Office Action, claims 1-16 and 18-22 were rejected under 35 U.S.C. 112, second paragraph for an alleged lack of distinctive language in the claims. The issue relates to the word, "derivative."

The rejection is traversed for the following reasons.

As argued in the record, an artisan familiar with chemistry in light of the teachings in the specification would understand the full scope of the term and the use thereof in the subject matter of interest. Nevertheless, solely for the purpose of advancing prosecution and not to be

interpreted as acquiescence to the position of the Examiner, a particular reagent is recited. The claims are clear and distinct, and an artisan would well be able to interpret the claims and to understand the metes and bounds thereof. Accordingly, withdrawal of the rejection is requested respectfully.

III. Beginning on page 9 of the Office Action, claims 1-16 and 18-22 were rejected under 35 U.S.C. 103(a) over Sommermeyer in view of Wilchek et al. and Cook, and further in view of Vallazza et al.

The Examiner relied on Sommermeyer for teaching HES conjugates, referring to paragraphs 25-26 of U.S. Publ. No. 2005/0063943. The Examiner noted that Sommermeyer does not require, for example, the nucleic acid to have an amino group.

The Examiner stated that Wilchek et al. teach activating a sugar with N,N'-disuccinimidyl carbonate to form a reagent that can react with an amine group.

Cook was alleged to teach dextran derivatives of polynucleotides, generally through a linker. The Examiner had noted that Cook does not teach a dry solvent, an aldonic acid ester, particular molar ratios thereof, HES, a spiegelmer or the MW of the oligonucleotide.

The Examiner relied on Vallazza et al. for teaching aptamers.

The Examiner then recited KSR for the proposition that mere substitution of reagents amongst the four references is predictable, despite the fact that the Examiner had admitted that the art is unpredictable, and the Examiner believed there is some motivation in the art to combine the teachings of the four references, seemingly without relying on hindsight.

Hence, the Examiner concluded that because the elements of the invention were known in the art, it would have been predictable to combine the elements to obtain the invention of interest.

The rejection is traversed for the following reasons.

As provided throughout the instant specification, and demonstrated in the working examples, the subject matter of interest improves on and/or overcomes the previously unsolved problem of conjugating a saccharide and a nucleic acid by providing a robust and reproducible method for making aldonic acid esters of a sugar, which then can react with a nucleophilic amine

group of a nucleic acid to produce a covalent bond and a conjugate between a sugar and a nucleic acid.

As noted on page 6 of the instant specification, surprisingly, the conditions and reagents taught in the instant specification enable a selective activation of carboxyl groups as compared to hydroxyl groups of a sugar, which produces the superior results obtained in the practice of the subject matter of interest.

Also as noted at pages 6 et seq. and in the working examples, known methods for conjugating a sugar primarily to polypeptides are inoperable with a nucleic acid. Thus, for example, a method using EDC is inoperable (see, for example, Example 4 of the instant application), even in high EDC excess because of, for example, interference contributed by the phosphate groups of nucleic acids.

Other prior art mechanisms also were found inoperable in conjugating sugar to nucleic acid, for example, using an imidazaole intermediate (for example, Example 12). Use of an active hydroxysuccinimide ester via a lactone (Example 11) was unsuccessful. A reductive amination scheme was unsuccessful.

Those comparative studies are set forth in Examples 4-14 and in Figure 2 of the instant application and provide the foundation to conclude that the prior methods used for polypeptides do not provide a predictable solution to the longstanding problem of finding a method for conjugating a sugar to a nucleic acid.

The majority of the teachings of Sommermeyer relates to proteins and small molecules, such as antibiotics. As noted in paragraphs 126-128 of the ‘943 publication, any known oxidizing scheme was purported to be usable, such as, using EDC (which applicant demonstrated was not usable with nucleic acids), a Schiff reaction and so on.

In the singular instance of Sommermeyer where conjugation to a nucleic acid was taught, Example 7 and Figure 10, the ‘943 publication teaches a particular mechanism relying on using an amino-modified HES and a thiolated nucleic acid where conjugation occurs in part through the sulfhydryl group. It can be seen that the steps in that process and the mechanism of reaction are distinguishable from the subject matter of interest.

The Examiner referred to paragraphs [0025] and [0026] of Sommermeyer which were alleged to teach oxidation of the reducing carbonyl group of the polysaccharide, ultimately to form a lactone.

However, as provided in the comparative testing of the instant application, methods relating to proteins do not translate to nucleic acids, and use of a mechanism relying on a lactone was shown to be ineffective to conjugate sugar to nucleic acid (Example 11 of the instant application).

The Examiner also indicated that paragraphs [0025] and [0026] of Sommermeyer teach DMSO. Although DMSO was used in that reaction relying on a lactone, the reagents used and the mechanism clearly are distinct from that taught in the instant application.

The published PCT referred to in paragraph 26 of the '943 publication corresponds to U.S. Pat. No. 6,083,909, which relates to conjugating sugar to hemoglobin. Oxidation of the sugar was obtained by treatment with iodine and KOH, last full paragraph of column 5. The '909 patent does not teach and does not appreciate the issues when dealing with polynucleotides.

Thus, there are fundamental differences between the chemistry of Sommermeyer, and teachings referred to therein, and of the instant application. The comparative studies provided in the instant specification demonstrate the methods of Sommermeyer to be inoperable or ineffective with nucleic acids.

The Examiner described the teaching of Wilchek et al. on page 11 as allegedly activating a polysaccharide with N,N'-disuccinimidyl carbonate.

However, the reaction described by Wilchek et al. is the very sort of reaction that is to be avoided. The present inventor found that under the particular reaction conditions of interest, surprisingly and unexpectedly what is activated is the carboxylic acid moiety rather than the hydroxyl group of a sugar, as taught by Wilchek et al., see the figure. It is activation of the carboxylic group that is decisive for the effective conjugation of the polynucleotide and the polysaccharide.

Thus, it is clear, Wilchek et al. teach away from the subject matter of interest. Because of that fatal deficiency of Wilchek et al., the rejection cannot stand because the combination of references teaches the opposite of what the instant invention obtains.

As noted at pages 9 and 10 of Cook, that reference teaches use of sugar hydroxyl groups for conjugation. However, as with Wilchek et al,, that is not what is practiced in the subject matter of interest, as taught in the first full paragraph of page 6 of the instant specification, no activation of sugar hydroxyl groups occurs in the practice of the method of interest.

Valazza et al. relate to aptamers. That reference does not relate to a method of conjugating a polysaccharide to a nucleic acid.

Thus, for a number of reasons, some of which are explained hereinabove, a prima facie case of obviousness has not been made as the aggregate teachings do not provide a method of conjugating a sugar and a nucleic acid with a reasonable expectation of success, teaching away by the cited references and so on.

Also, applicant wishes to reiterate there were numerous attempts to conjugate a polysaccharide to a polynucleotide prior to the instant invention, and all resulted in failure.

As noted in the first full paragraph on page 6 of the instant application, it was a surprise that activation of hydroxyl groups was not observed in the method of interest, as would be expected based on the prior art, such as, Wilchek et al. and Cook. Instead, a specific activation of the carboxyl group was observed. Further, as noted in the fourth full paragraph on page 6, prior art methods using carbodiimide, such as, EDC, were inefficient with polynucleotides because of, for example, the negative impact of phosphates and phosphate groups on such reagents. See also the third full paragraph of page 6 through the third full paragraph of page 7 for other examples recounting the lack of success with prior art materials and methods with regard to nucleic acids.

Clearly, contrary to the position of the Examiner, there is no predictability in the art with respect to applying prior art materials and/or methods for conjugating sugars to nucleic acids.

Combining prior art elements in asserted known methods did not yield a successful result. Simple substitution of one known element for another did not yield a successful result. Known techniques were inoperable for conjugating a polysaccharide with a polynucleotide. Hence, applying known methods to obtain the subject matter of interest met with failure. Because of those actual failures, there is no predictability in the art and there can be no finite and predictable solutions. Moreover, in view thereof, there are no predictable variations in the relevant art or in

a different art. Finally, there is no teaching or suggestion in the art to obtain the subject matter of interest.

Accordingly, the subject matter of interest neither was known nor suggested in the art. Moreover, there is no predictability in the art to have made or to render obvious the subject matter of interest of conjugating sugar and nucleic acid.

Thus, for those additional reasons, a prima facie case of obviousness has not been made.

Those prior failed attempts also provide a basis to overcome any asserted case of obviousness. The instant subject matter of interest addressed those prior failed attempts with the successful conjugation of sugar and nucleic acid.

The subject matter of interest also satisfied a long unmet need, that is, the use of carbohydrates on nucleic acids to obtain, in principle, the benefits observed by conjugating sugars to polypeptides.

Accordingly, not only is a prima facie case of obviousness not been made, for example, the teaching away of Wilchek et al. and Cook that makes the cited combination of references insufficient, or because of the lack of predictability to obtain the subject matter of interest, but, those secondary considerations of prior failed attempts and satisfaction of a long unmet need demonstrate the non-obviousness of the subject matter of interest.

Finally, even if arguendo, one were to hypothesize a prima facie case of obviousness were made, the results of the comparative studies provided in the instant specification where the teachings of the closest prior art, Sommermeyer, were compared to the subject matter of interest, overcome any such asserted case of obviousness. Thus, for example, Sommermeyer teach EDC in the '943 publication. Examples 4-10 of the instant application demonstrate that EDC is essentially inoperable for conjugating sugar and nucleic acid.

That comparative data with the closest prior art overcomes any asserted case of obviousness over Sommermeyer and is but another reason substantiating the non-obviousness of the subject matter of interest.

Accordingly, withdrawal of the rejection is requested respectfully.

CONCLUSION

Applicant has taken steps to place the application in condition for allowance. Reexamination, reconsideration and withdrawal of the rejections are requested respectfully. Favorable consideration and early indication of allowance are solicited earnestly. If any questions remain, those can be directed to the undersigned at the local exchange noted below.

Respectfully submitted,

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Dated: 14 November 2011